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Stereoelectronic Model to Explain Highly Stereoselective Reactions of Seven-membered Ring Oxocarbenium Ion Intermediates

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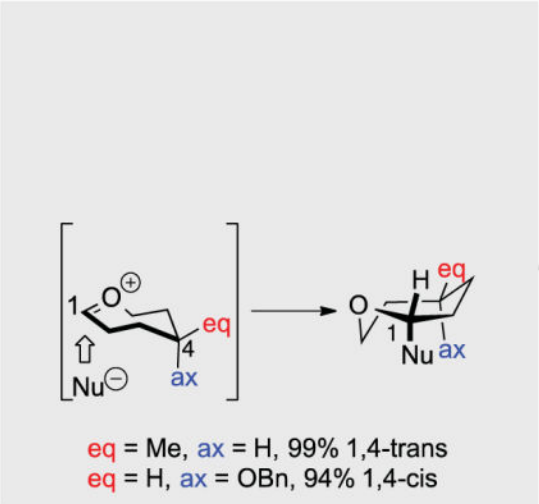
Abstract

Nucleophilic attack on seven-membered ring oxocarbenium ions is generally highly stereoselective. The preferred mode of nucleophilic attack forms the product in a conformation that minimizes transannular interactions, leading to different stereoselectivities compared to reactions involving six-membered ring oxocarbenium ions.

Graphical Abstract



Keywords

carbocations; stereoselectivity; conformational analysis; electrostatic effects; carbohydrates

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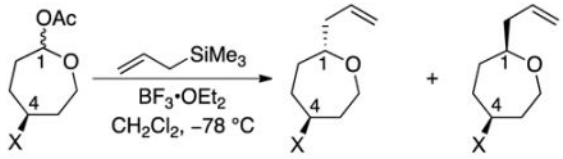
Supporting information for this article is given via a link at the end of the document.

Because of their biological significance and the challenges inherent to the synthesis of medium-ring compounds,[1] seven-membered ring ethers (oxepanes) represent important synthetic targets.[1–2] Substitution reactions of oxepane acetals, which likely proceed through oxocarbenium ion intermediates, are particularly useful methods for the stereoselective construction of natural products and seven-membered ring sugar derivatives.[3] The origin of stereoselectivity in these transformations remains poorly understood, however, because of the conformational complexity of seven-membered ring systems.[4–5] No systematic study of the nucleophilic additions to simple seven-membered ring oxocarbenium ions has appeared, and no general explanation has been forwarded to understand the reactions of these intermediates.[6]

We report here that nucleophilic substitution reactions of oxepane acetals are highly stereoselective in most cases. We propose a model to explain these selectivities by considering that nucleophilic attack should occur from the face that minimizes transannular interactions in the first-formed product. We also demonstrate that acetal substitution reactions that proceed by S_N2-like mechanisms result in products with the opposite stereochemical configurations compared to the S_N1-like reactions.

Initial studies revealed that nucleophilic substitution reactions of acetals that proceed via seven-membered ring oxocarbenium ions are highly diastereoselective. Under dissociative (S_N1-like) conditions, the substitution reaction of acetal **1** (X = Me) occurred with high trans selectivity [Eq. (1)].[7] By contrast, the substitution reaction of alkoxy-substituted acetal **1** (X = OBn) gave the product with the opposite relative stereochemistry.[8–9] These selectivities are also opposite to what is observed in reactions of six-membered ring oxocarbenium ions:[8] in the six-membered ring series, the alkyl-substituted acetal favored the 1,4-cis product, and the alkoxy-substituted acetal formed the 1,4-trans product.



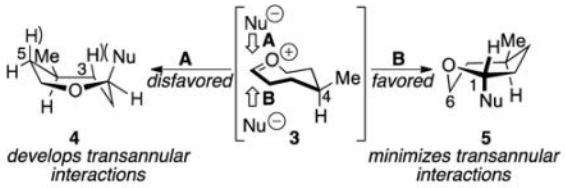
X	*trans*-**2** : *cis*-**2**
Me	99 : 1
OBn	4 : 96

(1)

Because the diverging stereochemical outcomes illustrated in Equation 1 are similar to observations regarding the reactions of five- and six-membered ring oxocarbenium ions,[8–9] the factors that govern selectivities in those systems should apply to the seven-membered ring system. Models used to explain selective reactions of oxocarbenium ions and iminium ions[8–12] consider the conformations of these reactive intermediates and how those conformations change in the transition state of nucleophilic attack which, in the case of π-

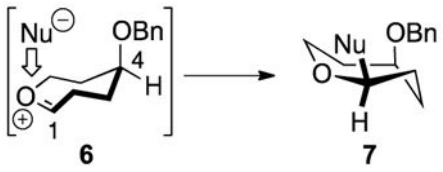
nucleophiles, is irreversible.[13] Although it would be desirable to model this step step computationally,[14] calculations involving interactions of cations with electron-rich species are challenging.[15–17] Nevertheless, models derived by conformational analysis of the first-formed products that result from nucleophilic attack can be useful.[9,11–12]

A model to explain and predict the outcomes of reactions involving seven-membered ring oxocarbenium ions is illustrated for oxocarbenium ion **3** [Eq. (2)]. The oxocarbenium ion likely adopts a chair-like conformation[18] with the methyl group in a pseudoequatorial position.[19–20] Steric interactions between the approaching nucleophile and the substituent should be minimal, so the major product is likely to be formed from this lowest energy conformer.[21] The two different modes of nucleophilic attack, **A** and **B**, give the products in twist-chair-like conformations, but the interactions that develop in the two transition states are different. Nucleophilic attack along trajectory **A** would pyramidalize the carbon and oxygen atoms in opposite directions,[8,12] leading to the initial conformation of the product **4** in a twist-chair conformation (the TC6 conformation[5]). Conversely, attack along trajectory **B** would form the product **5** in a different twist-chair conformation (TC5). Attack by mode **B** is preferred because the resulting product is formed with the carbon atom bearing the nucleophile in a position that minimizes steric interactions.[22] In the first-formed product **5**, the nucleophile and the hydrogen atom at C1 would occupy isoclinal positions, so neither group is axial. As a result, steric interactions with the other atoms of the ring are minimized.[4] By contrast, conformer **4** is higher in energy because it places C1 in a more sterically hindered position,[4] with destabilizing interactions between the nucleophile and axial hydrogen atoms at C3 and C5 [Eq. (2)].[4–5,22] As a result, the transition state leading to conformer **4** should be higher in energy than the one leading to **5**.[23–24]



(2)

The preferred attack on the oxocarbenium ion along trajectory **B** also explains the selective formation of the 1,4-cis product when an alkoxy group is located at C4. The cation should adopt a pseudoaxial conformation **6** [Eq. (3)] to maximize electrostatic attraction between the positively charged carbon atom and the partially negatively charged oxygen atom of the benzyloxy group.[8,16,25–26] Computational studies reinforce this prediction: **6** was calculated to be favored by 1.4 kcal/mol compared to an equatorial conformer.[19] Nucleophilic attack from the torsionally favored direction would form the 1,4-cis product in the preferred twist-chair conformation (**7**).

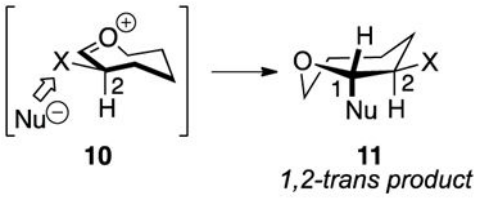


(3)

Other results support the prediction that the favored transition state for nucleophilic attack develops the fewest transannular interactions. Nucleophilic additions to oxocarbenium ions bearing an alkyl or an alkoxy group at C2 are highly trans-selective [Eq. (4)], in contrast to results with five- and six-membered ring acetals, where selectivity is low.[8–9] These reactions likely proceed via the equatorially substituted oxocarbenium ion **10** [Eq. (5)]. In the case of X = OBn, this conformation, which computational studies indicate is favored by 2.5 kcal/mol,[19] maximizes hyperconjugative stabilization from the pseudoaxial $\sigma_{C\text{-}H}$ orbital.[8,16] Attack along the preferred trajectory leads to the twist-chair product **11**.[27]

X	diastereoselectivity
Me	≥97: 3
OBn	≥97 : 3

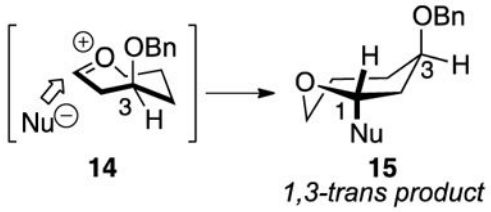
(4)



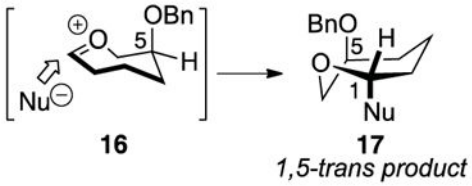
(5)

Considering the importance of seven-membered ring sugars in glycobiology,[2,28] we examined the substitution reactions of two additional alkoxy-substituted seven-membered ring acetals (Chart 1). The lower selectivity for the formation of the 1,3-trans product *trans*-**12** likely results from the low axial preference for the oxocarbenium ion **14** (calculated to be 0.3 kcal/mol[19]) due to competing electrostatic stabilization and steric destabilization

[Eq. (6)]. The selectivity observed for the formation of *trans*-**13** results from the preference[8–9,16,25–26] for the alkoxy group to adopt a pseudoaxial orientation in the oxocarbenium ion **16** [Eq. (7)], which is consistent with the calculated preference of 0.8 kcal/mol for this conformer.[19]

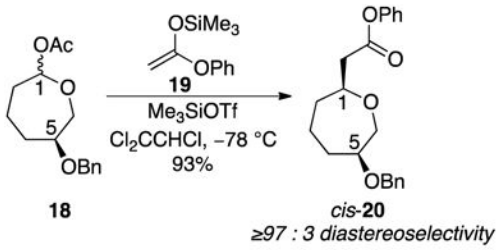


(6)



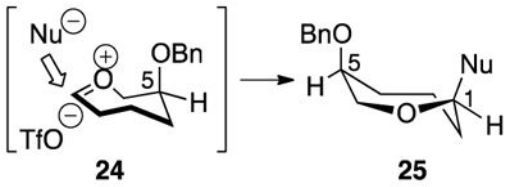
(7)

Because many substitution reactions in carbohydrate chemistry utilize stronger nucleophiles with either ion pairs or covalent intermediates,[29–31] we examined reactions under similar conditions. Using a highly reactive nucleophile (silyl ketene acetal **19**) in the presence of triflate ions in a non-polar solvent (trichloroethylene)[31] gave the cis isomer [Eq. (8)].[32] The relative configuration of the product is opposite to what was observed for the allylation (Chart 1). the switch in selectivity for the S_N2-type *C*-glycosylation reactions compared to S_N1-type reactions, which was observed for reactions of 2- and 3-alkoxyoxepane acetals (*cis*-**21** and *cis*-**22**, Chart 2), parallels observations in six-membered ring systems.[31] In the case of the 4-benzyloxy acetal **1** (X = OBn), however, the cis isomer is the major product regardless of reaction manifold (*cis*-**2**, [Eq. (1)], and *cis*-**23**, Chart 2). The benzyloxy group at C4 may be too far from the oxygen and carbon atoms of the oxocarbenium ion intermediate to destabilize it inductively,[33] so reactions proceed via oxocarbenium ions even in the presence of the triflate ion.[31]



(8)

The selective substitutions to form *cis*-**20**, *cis*-**21**, and *cis*-**22** are consistent with the stereochemical model adapted for reactions under S_N2-like conditions.[31] As illustrated for the preparation of *cis*-**20**, a contact-ion pair between the oxocarbenium ion and triflate anion, **24** (or the anomeric triflate[29–30]), would position the triflate where the nucleophile would attack the free ion [Eq. (9)].[31] Displacement of the triflate would occur from the opposite face, leading to the observed products.



(9)

In conclusion, the substitution reactions of seven-membered ring acetals occur with generally high diastereoselectivity, regardless of whether reactions involve free ions or intermediates with close contact between the electrophile and the leaving group. The reactions are selective because of strong conformational preferences of oxepanes, which favor one conformer of the product as it is formed upon nucleophilic attack.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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19. Density functional theory calculations (B3LYP) were performed using Gaussian 09 with the 6-31+G** basis set with CH_2Cl_2 as implicit solvent. Details of all computational studies are provided as supporting information.
20. Calculations indicate that the equatorial oxocarbenium ion **3** is favored over the axial conformer by 2.4 kcal/mol.
21. In cases where the nucleophile approaches a substituent closely, such as C2-substituted systems, transition state effects can be important (see, for example, reference 8).
22. The computed structures for **4** and **5** (Nu = Me) illustrate the different steric interactions in the two conformers. In **4**, transannular interactions occur between the nucleophile and two hydrogen atoms of the ring. The distance between the carbon atom of Nu and H3 is 2.71 Å, and the distance to H5 is 2.88 Å. In **5**, there is only one transannular interaction (with H6), and the distance is 2.90 Å.
23. A model assuming that selectivity is controlled by attack trans to the axial hydrogen atom at C3 would not be consistent with the models used to explain selectivities in five- and six-membered ring systems (references 9 and 12).
24. Computational studies also suggest that attack by mode **B** should be favored. A methyl group was used as the carbon nucleophile to simplify the calculation. The twist-chair isomer **5** was found to be lower energy than **4** by 4.7 kcal/mol, so transition states leading to this conformer should be lower energy.
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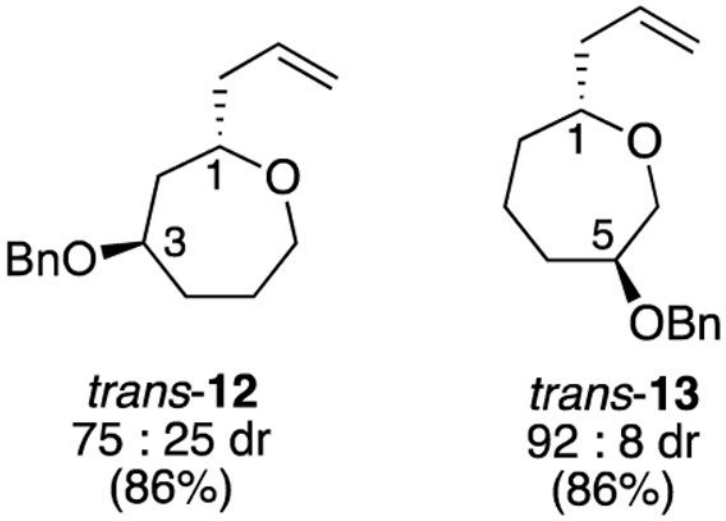

trans-**12**
75 : 25 dr
(86%)

trans-**13**
92 : 8 dr
(86%)

Chart 1.

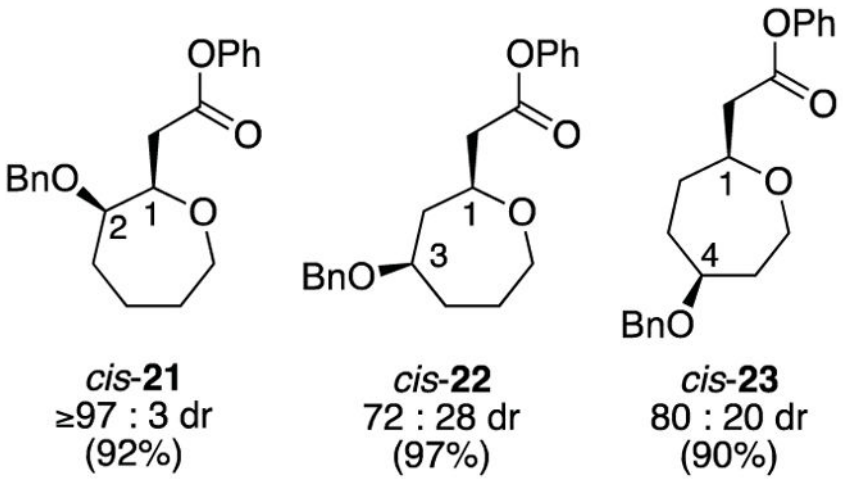

Chart 2.